

156A ABSTRACTS - Cardiac Function and Heart Failure

JACC

March 19, 2003

of CHF pts more responsive to this stimulus. Furthermore, TGF β 1 was the most potent stimulus for collagen production in human VFs. These data suggest that factors thought to be activated in the setting of CHF such as LPS may increase collagen production via downstream induction of TGF β 1, which we have shown to be potentially pro-fibrogenic within the heart.

1060-68

Negative Inotropic Effect of Troponin I Phosphorylation by P38 MAP Kinase

Hong Kan, Sherry Xie, Mitchell S. Finkel, West Virginia University, Morgantown, WV

Background: Evidence continues to accumulate that the host response to ischemia and infection share common signaling pathways involving cytokines, nitric oxide (NO) and mitogen activated protein (MAP) kinase. P38 MAP kinase is a member of this class of intracellular enzymes that are activated in response to a variety of stresses including ischemia and infection. We previously reported that HIV gp120 enhanced IL-1 β stimulated inducible nitric oxide synthase (iNOS; NOS II) mRNA, protein and NO production by neonatal rat cardiac myocytes through a p38 MAP kinase mediated mechanism. This initial observation in neonatal myocytes prompted us to explore the direct inotropic effects of gp120 on isolated adult rat ventricular myocytes (ARVM).

Methods: ARVM were continuously superfused with gp120 (1 μ g/ml) and percentage fractional shortening (FS) determined by automated border detection and simultaneous intracellular ionized free calcium ([Ca $^{++}$]) measured by fura-2AM (2 μ M) fluorescence.

Results: Gp120 alone increased FS and increased [Ca $^{++}$] at 2-20 min and then depressed FS with no change in [Ca $^{++}$] at 1-2 hrs (N=9; p<0.01). P38 MAP kinase activation was noted at 10 min to 2 hrs associated with phosphorylation of Troponin I (Tn I). Inhibition of p38 MAP kinase activation and Tn I phosphorylation by SB203580 (10 μ M) completely prevented the delayed negative inotropic effect of gp120 (N=9; p<0.01).

Conclusion: We conclude that HIV gp120 directly regulates ARVM through an initial Ca $^{++}$ dependent positive inotropic effect followed by a Ca $^{++}$ independent negative inotropic effect mediated by p38 MAP kinase phosphorylation of Tn I. P38 MAP kinase has been implicated in ischemic pre-conditioning and adrenergic signaling in the heart. Thus, activation of this signaling pathway by infection and/or ischemia may contribute to myocardial dysfunction in HIV and other non-ischemic as well as ischemic cardiomyopathies.

1060-69

Dyspnea-Induced Training of the Diaphragm Augments Local Antioxidative Enzyme Activity in an Animal Model of Heart Failure: Implications for Aerobic Metabolism

Stephan Gielens, Bettina Riedel, Volker Adams, Axel Linke, Gerhard Schuler, Rainer Hambrecht, University of Leipzig - Heart Center, Leipzig, Germany

Background: Exercise training has been shown to enhance local skeletal muscle antioxidative enzyme capacity. In chronic heart failure (CHF) the diaphragm is also subjected increased activity due to tachypnea. Aim of this study was to determine whether the diaphragm as a skeletal muscle would show a similar increase in antioxidative enzyme activity as a result of the dyspnea-related training effect as opposed to the untrained quadriceps.

Methods: Male Wistar Kyoto rats (250 g) were subjected to LAD ligation (MI, n=19) or sham operation (S, n=9). After 12 weeks left ventricular function was analyzed by echocardiography and LV catheterization with a 2F micromanometer-tipped catheter. Catalase, superoxide dismutase (SOD), and glutathione peroxidase (GPX) activities were measured photometrically and their expression assessed by quantitative RT-PCR (Light-Cycler). Local cytochrome c oxidase (COX) activity was quantified by the Clark oxygen electrode.

Results: After 12 weeks MI rats showed significant LV contractile dysfunction (dp/dtmax: 4.47 \pm 0.24 versus 6.03 \pm 0.42 mm Hg/ms, p=0.003). GPX activity (91.8 \pm 4.0 versus 67.4 \pm 5.71 mU/mg in S, p=0.002) and MnSOD activity (2.0 \pm 0.3 versus 0.6 \pm 0.24 %inhib/ μ g in S, p=0.009) were both significantly elevated in the diaphragm. This trend was also evident in diaphragmatic GPX expression (117 \pm 40 versus 89 \pm 19 in S, p=NS). Catalase and Cu/Zn SOD activity and expression were unchanged. COX activity in the diaphragm was largely unchanged (126.9 \pm 11.06 versus 156.0 \pm 17.13 nmol O $_2$ /min mg in S, p=NS), in contrast, it was reduced in the quadriceps (67.81 \pm 7.98 versus 130.5 \pm 18.43 nmol O $_2$ /min mg in S, p=0.001).

Conclusion: In experimental heart failure the dyspnea-related increase in diaphragm muscle activity is associated with increased activity of key antioxidative enzymes (GPX, Mn SOD). While COX activity was significantly reduced in the peripheral skeletal muscle it remained unchanged in the diaphragm. The increased antioxidative protection may modify the vulnerability of the aerobic energy metabolism in the diaphragm to toxic inflammatory nitric oxide production in CHF by reducing peroxynitrite generation.

POSTER SESSION

1061 Obesity/Cachexia and Other Metabolic Factors

Sunday, March 30, 2003, 3:00 p.m.-5:00 p.m.

McCormick Place, Hall A

Presentation Hour: 4:00 p.m.-5:00 p.m.

1061-70

Leptin and the Ventilatory Response to Exercise in Heart Failure

Robert Wolk, Bruce Johnson, Virend K. Somers, Mayo Clinic, Rochester, MN

BACKGROUND: Exercise-induced hyperventilation is a negative prognostic factor in heart failure (CHF). Studies in transgenic animals suggest that leptin, a hormone secreted by adipocytes, contributes to the regulation of respiration. Plasma leptin levels are elevated in non-cachectic CHF. We tested the hypothesis that leptin is involved in the regulation of ventilatory responses to exercise in CHF. **METHODS:** We studied 50 patients with stable CHF without cachexia. All subjects underwent anthropometric measurements, resting echocardiography, pulmonary function tests and a cardiopulmonary exercise test. The ventilatory response to exercise was assessed by calculating the VE/VCO $_2$ and VE/VO $_2$ slopes (VE - ventilation per unit time, VCO $_2$ - carbon dioxide production, VO $_2$ - oxygen consumption). **RESULTS:** Using a multiple regression model, leptin was significantly and positively correlated with both VE/VCO $_2$ slope (regression coefficient=0.77, F=21.33, p<0.001) and VE/VO $_2$ slope (regression coefficient=0.76, F=12.39, p=0.001). This correlation was independent of age, gender, BMI, body fat, ejection fraction, pulmonary function, plasma norepinephrine levels, and medications. VE/VCO $_2$ slope was strongly correlated with leptin even when VE/VO $_2$ slope and peak VO $_2$ entered the model as independent variables (regression coefficient=0.41, F=7.46, p=0.01). In contrast, leptin was not a predictor of VE/VO $_2$ slope independent of VE/VCO $_2$ slope. **CONCLUSIONS:** Leptin is a powerful and independent predictor of VE/VCO $_2$ slope in heart failure, and may be a link between metabolic, cardiovascular and respiratory abnormalities in CHF. Because elevated VE/VCO $_2$ is an important prognostic factor in CHF, plasma leptin may also provide a valuable, easily measured, and economic marker for risk stratification in the CHF population.

1061-71

Increasing Body Mass Index Is Associated With Decreased Myocardial Efficiency in Young Women

Linda R. Peterson, Alan D. Waggoner, Pilar Herrero, Susan Racette, JoAnn Marsala, Tim Meyer, Samuel Klein, Victor G. Davila-Roman, Robert J. Gropler, Washington University, St. Louis, MO

Background: Obesity is a risk factor for heart failure with women being at higher risk than men. Animal models of obesity demonstrate decreased myocardial efficiency, which is a hallmark of heart failure. The effect of increasing obesity as measured by body mass index (BMI) on myocardial efficiency in humans is not known. **Methods:** We studied 19 healthy women, 7 lean (BMI 21 \pm 2 kg/m 2 ; mean \pm std) and 12 obese (BMI 32 \pm 6). All were normotensive, nondiabetics and had a normal echocardiogram. After a 12 hour fast, myocardial oxygen consumption (MVO $_2$) was measured by positron emission tomography (PET) with C-11 acetate. Left ventricular (LV) systolic function, mass, & stroke volume were assessed using echocardiography after the PET scan. Hemodynamics were monitored during the PET scan and echocardiogram. Efficiency per gram of LV was calculated as systolic blood pressure (SBP x stroke volume indexed for body surface area (SVI))/(MVO $_2$ x LV mass).

Results:

| | Age | SBP | HR | SVI | LV | MVO $_2$ | Efficiency (mm Hg x |
|-------|----------|-----------|------------|----------|-----------|-----------------|----------------------------|
| | | (mm | (bpm) | (ml/ | mass | μ mol/g/min | ml)/(μ mol x m 2) |
| | | Hg) | | mL) | (g) | | |
| Lea | 24 \pm | 108 \pm | 65 \pm 7 | 39 \pm | 120 \pm | 5.2 \pm 1.0 | 454 \pm 144 |
| n | 4 | 11 | | 4 | 26 | | |
| Obese | 30 \pm | 118 \pm | 74 \pm | 34 \pm | 159 \pm | 5.9 \pm 1.0* | 339 \pm 138†† |
| se | 5* | 14 | 10** | 5 | 28† | | |

*p < .01 versus lean, **p = .06, †p < .005, ††p = .10

Obese women had a higher MVO $_2$ & a higher LV mass. Although efficiency was not significantly different between the 2 groups, efficiency correlated with BMI (r=.45, p=.06).

Conclusions: Myocardial efficiency per gram of LV decreases with increasing BMI in young, otherwise healthy women. Although it requires future study, these data suggest that decreasing efficiency may lead to or be a marker of future cardiac dysfunction in young otherwise healthy women.

1061-72

Prevention and Reversal of Cachexia in Patients With Chronic Heart Failure by Bisoprolol: Results From the CIBIS-II Study

Stefan D. Anker, Philippe Lechat, Henry J. Dargie, for the CIBIS-II Investigators, Charité Medical School, Berlin, Germany, Western Infirmary, Glasgow, United Kingdom

Background: Cachexia is common in chronic heart failure (CHF), is associated with increased morbidity and fails to respond to conventional treatments. It is not known, whether the selective beta-1-receptor blocker bisoprolol has an effect on cachexia development in CHF.

Methods: In a retrospective analysis of the CIBIS-II trial, we evaluated the impact of